REMARKS

Applicants have amended claims 21 and 28 to make clear that the recited cells express ALK-1. Support for these amendments is found on page 36, last paragraph to page 38, line 9 wherein applicants disclose using cells that express ALK-1 to identify genes regulated by Smad-1.

Claims 21-23 and 26 stand rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by either Yingling or Lechleider. In view of the amendments to the claims and the following remarks applicants respectfully request that the Examiner reconsider and withdraw the rejection.

> "Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention."

Rockwell International Corp. v United States, 47 USPQ 2d (Fed. Cir. 1998)

Applicants' amended claim 21 requires that the cell expresses ALK-1. Claim 24 requires that the molecule is a portion of TGF-β sufficient to bind to ALK-1. Applicants have demonstrated that in the absence of ALK-1 Smad-1 is not phosphorylated in response to TGF-β (page 35, line 20 to page 36, line 10). In addition, ALK-1 is an endothelial cell type I receptor for the TGF-β superfamily of ligands (See, e.g, Klaus et al., "Novel missense and frameshift mutations in the activin receptor-like kinase-1 gene in hereditary hemorrhagic telangiectasia" *Hum. Mutat.*, 1998; 12 (2): 137, abstract). The experiments described by Lechleider or Yingling do not use endothelial cells. A549 adenocarcinoma cells (Lechleider) are epithelial cells and Yingling's experiments use either epithelial cells (NmuMg) and myoblasts (L6)(page 8940). In addition, Anita B. Roberts and Robert J. Lechleider, two authors of Lechleider cited by the Examiner, state that those of skill in the art appreciate that Smad-1 is not the phosphorylated Smad detected by Yingling and Lechleider (see ¶ 2 of the Declaration of Anita B. Roberts and Robert J. Lechleider submitted with applicants' May 2, 2000 response). As such, Yingling and Lechleider do not teach a method that requires the

use of cells expressing ALK-1 nor do they teach that Smad-1 is phosphorylated in response to TGF-β. Thus, neither Yingling or Lechleider anticipate the invention as claimed.

In view of the amendments to the claims and the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b).

Claim 24 stands rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over either one of Yingling or Lechleider. In view of the amendments to the claims applicants respectfully request that the Examiner reconsider and withdraw this rejection.

> "[A] proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . .Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."

In re Vaeck, 20 USPQ2d 1438, 1442 (CAFC 1991)

The amended claims require that the claims express ALK-1 and that the agent binds to ALK-1. In order for the agent to bind to ALK-1 resulting in phosphorylation of Smad-1, ALK-1 must be expressed by the cell. As discussed previously, ALK-1 is an endothelial cell type I receptor (Klaus et al., 1998 supra) whereas the cells used in the experiments described by Yingling and Lechleider are not endothelial cells, but are rather epithelial cells or myoblasts. Two of the authors of Lechleider state that those of skill in the art appreciate that Smad-1 is not phosphorylated in the experiments described in Lechleider or Yingling (see ¶ 2 of the Declaration of Anita B. Roberts and Robert J. Lechleider submitted with applicants' May 2, 2000 response). Therefore, both references fail to teach or suggest cells expressing ALK-1 or that ALK-1 phosphorylates Smad-1. Both references also fail to teach or suggest contacting cells that express ALK-1 with an agent that binds to ALK-1 to phosproylate Smad-1. Therefore, one of skill upon reading Lechleider or Yingling

would have no motivation to contact particular cells, i.e., those expressing ALK-1, with a portion of TGF-β sufficient to bind to ALK-1; Nor would one of skill in the art have any reason to expect that treating cells expressing ALK-1 with a portion of TGF-β sufficient to bind to ALK-1 would result in the phosphorylation of Smad-1. Thus, Yingling and Lechleider, alone or in combination, fail to satisfy the requirements of § 103.

In view of the amendments to the claims and the foregoing remarks applicants respectfully request the Examiner to reconsider and withdraw the rejection of claim 24 under 35 U.S.C. § 103(a).

Claim 28 stands rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by Ladher. In view of the amendments to the claims applicants request that the Examiner reconsider and withdraw the rejection.

Applicants amended claim 28 requires that the first sample of cells expresses both ALK-1 and Smad-1 and that the agent binds to ALK-1 to inhibit or activate phosphorylation of Smad-1. Ladher does not disclose that BMP-4 binds to ALK-1 to inhibit or activate the phosphorylation of Smad-1. Therefore Ladher does not satisfy the requirements of § 102 because Ladher fails to teach every limitation of the claims (see *Rockwell International Corp. v United States,* 47 USPQ2d (Fed. Cir. 1998)). Thus Ladher does not anticipate the invention as claimed.

In view of the amendments to the claims and the foregoing remarks applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 28 under 35 U.S.C. § 102(b).

The Examiner contends that the application is not in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. In particular, the Examiner contends that the specification purportedly does not recite the appropriate sequence identifiers at each place where a sequence is discussed. Applicants have amended the application to identify the disclosed sequences by their respective SEQ ID NOS wherever they appear and have provided a paper copy and a computer readable form of the sequence listing, as well as a statement pursuant to 37 C.F.R. § 1.821 (f) and (g).

This application is in condition for allowance and early notice of the same is respectfully requested. Should the Examiner have any questions, comments or suggestions, he is invited to contact Applicant's representative at the number indicated below.

The Commissioner is hereby authorized to deduct any missing or insufficient fees associated with these papers from deposit account deposit account 06-2375 under Order No. 09905178.

Respectfully submitted,

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